

Stopping Alzheimer's disease before it starts ^[1]

Discovery ^[2]

Jamie Tyrone got her first look at Alzheimer's disease at the age of 10, in the mid-1970s, during a visit with her great-grandmother. "She was lifeless," Tyrone recalls. "Her eyes were empty."

Nearly four decades later, Tyrone signed up for an online research study to learn about her genetic risk for 23 diseases. Alzheimer's disease didn't even cross her mind. When she received results pointing to a 91% lifetime risk of Alzheimer's disease, she was devastated. But what shook Tyrone most deeply was that, despite this knowledge, she was powerless. There are no proven ways to prevent Alzheimer's disease.

Now, however, a new clinical trial is in the works that will test two experimental treatments from Novartis in individuals who have an elevated risk of developing Alzheimer's disease due to their genetic make-up and age. Although Tyrone is too young to participate in the trial, she plans to follow its progress. Preliminary research suggests that these treatments may prevent or delay the onset of symptoms. The trial—which was jointly designed by teams at Novartis and the Banner Alzheimer's Institute in Phoenix, Arizona—is unusual because of its focus on preventing the disease in older adults.

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"To be at this stage now where we can design a prevention trial that matches people with genetic risk to innovative therapies is a dream come true," says J. Michael Ryan, who is the Novartis Pharmaceuticals Neurodegeneration Therapeutic Area Head overseeing efforts to develop new Alzheimer's treatments at the company.



If successful, the trial could bring hope to Tyrone and others like her. Tyrone tested positive for two copies of a gene variant called APOE4, which is associated with an elevated risk of late-onset Alzheimer's disease. Tyrone, whose father died with Alzheimer's disease three years ago, got a copy from each parent. She has the same genetic profile as patients who will be enrolled into the Novartis-Banner trial. If preventive therapies prove effective, they would give Tyrone a way to take action to lower her Alzheimer's disease risk, similar to the way people use statins and aspirin to lower their heart disease risk.

The Need for Prevention

There are approximately 44 million people worldwide with dementia, according to Alzheimer's Disease International, with about 50-60% of these cases caused by Alzheimer's disease. That number is expected to triple by 2050 as the world's population continues to age. Costs of dementia care—which reached \$604 billion worldwide in 2010—are also expected to skyrocket. In the US alone, the cost is expected to rise to \$1.1 trillion by 2050, up from \$226 billion today, according to the Alzheimer's Association.

So far, no drugs have been proven to slow or prevent Alzheimer's disease. The treatments under investigation at Novartis target the amyloid cascade ^[3], the biological process that many scientists believe drives the disease. It begins when a toxic form of a protein called amyloid clumps in the brain and forms plaques. Scientists have not definitively proven that the cascade causes Alzheimer's, but so far evidence suggests that amyloid buildup may eventually trigger other processes that kill neurons and cause memory and thinking problems. "With the growing number of people living longer, this one age-related disease is projected to take a financially overwhelming toll on the world before today's 30-year-olds become senior citizens," says Eric Reiman, Executive Director of the Banner Alzheimer's Institute.

In the past, most drug trials—including those testing treatments that target the amyloid cascade—have focused on people who have already been diagnosed with the symptoms of Alzheimer's disease. But amyloid plaques may begin forming 20 years before symptoms appear. This new prevention trial aims to test drugs that could reduce or eliminate toxic amyloid early in the disease process, potentially stopping Alzheimer's before it starts.

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Targeting the Roots of Disease

The two experimental agents Novartis will test in the prevention trial are both the products of 15 years of research.

One targets a molecular machine in the brain called BACE-1. Part of this machine acts as scissors that cut up neuronal membrane proteins for disposal. This snipping process creates amyloid fragments, some of which might cause Alzheimer's. The Novartis treatment is designed to jam up the scissors to reduce and possibly eliminate the formation of toxic types of amyloid.

Early clinical testing suggests that the experimental therapy is entering the brain and jamming the scissors. Also, its activity appears to be limited to the BACE-1 scissor mechanism, which bodes well for safety.

"We will need to treat healthy people with this compound for a very long time," says Michael Ufer, a clinical pharmacologist and senior investigator in translational medicine at the Novartis Institutes for BioMedical Research. "This means the safety profile is key."

The other experimental treatment to be tested in the trial is an active immunotherapy drug. A small, harmless segment of the toxic amyloid protein is injected into the body. The immune system then responds naturally by producing antibodies that recognize the amyloid protein and act to clear it.

This experimental immunotherapy also appears to be hitting its target. In a phase 2 clinical trial, the team used positron emission tomography (PET) scans to measure amyloid plaques in the brain. They found that as the immune system responds to the treatment, the burden of brain amyloid decreases.

Designing a Trial for Prevention

The upcoming prevention trial aims to recruit people aged 60 to 75 who have two copies of the APOE4 gene variant and are still cognitively healthy. These individuals are quite likely to develop the first symptoms of Alzheimer's within five years, so it may be possible for the researchers to tell if their experimental therapies delay the disease when compared with a placebo.

These individuals might also benefit from therapies designed to eliminate or clear amyloid because research suggests that people with the APOE4 variant do not effectively clear amyloid from the brain. As a result, toxic amyloid is more likely to clump, form plaques, and potentially cause irreversible neurodegeneration. The people this trial is recruiting are likely already accumulating amyloid in their brains and forming plaques that could begin to disrupt brain function at any time.

"These people could potentially benefit from a prevention trial, given their risk and given what

we know about how APOE4 drives part of the amyloid cascade,” says Ana Graf, Global Program Head for the two experimental treatments at Novartis Pharmaceuticals in Basel, Switzerland.

Recruitment for the trial is scheduled to begin before the end of 2015. Banner and Novartis have collaborated to design a genotyping process [4] to enroll 1,300 high-risk individuals. The process employs a registry run by Banner that allows people who are interested in participating in Alzheimer’s research to sign up to receive notices of upcoming trials and be matched to appropriate trials based on their genotype.

One key priority of this program is to make sure that no one learns of his or her Alzheimer’s risk in the unexpected way Tyrone did.

For Tyrone, news of the trial was thrilling. She wanted to sign up immediately, but soon learned that, at age 55, she is too young to participate. Still, she is hopeful. “If this study has a positive outcome, I will be the first to go on the medication, even though I’m asymptomatic,” she says. “That’s the whole point.”

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